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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/723,308	11/26/2003	Henrik H. Jacobi	04305/100M285-US1	6838

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EXAMINER	
CHOI, FRANK I	
ART UNIT	PAPER NUMBER
1616	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/723,308	JACOBI ET AL.	
	Examiner	Art Unit	
	FRANK I. CHOI	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2008*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *91-95,97-105,130-180,183-198,203-205 and 213-244* is/are pending in the application.

4a) Of the above claim(s) *91-95,132-180 and 183-192* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *97-104,130,131,193-198,203-205 and 213-244* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The claimed invention is directed to a fast dispersing solid oral mucosal matrix containing grass pollen allergen which is several doses and kits and has the same dosage in each dose.

Claims 97-104, 130, 131, 193-198. 203-205, 213-244 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/61117 in view of Roser et al. (US Pat. 5,762,961), Cho et al., Remington's, Cleland et al., Pradalier and Hordijk et al..

WO 00/61117 discloses a fast-dispersing dosage form comprising a carrier containing fish gelatin and active ingredient (Page 6). It is disclosed that "fast-dispersing dosage form" refers to composition which disintegrate or disperse within 1-60 seconds, preferable 1 to 30 seconds, more preferable 1 to 10 seconds and particularly 2 to 8 seconds after being placed in the oral cavity (Page 7, lines 14-20). It is disclosed that the composition can be prepared as a solid dosage form prepared from a mold (Page 8). It is disclosed that the composition can contain other matrix forming agents, such as gums, polysaccharides, etc. and other materials such as mannitol, dextrose, lactose, galactose, trehalose, aluminum silicates, etc. (Page 10). It is disclosed that secondary components can be added such as preservatives, antioxidants, surfactants, viscosity enhancers, coloring agents, flavoring agents, pH modifiers, sweeteners and

taste masking agents can be added (Page 11, lines 4-15). It is disclosed that active ingredients include antacids, such as aluminum hydroxide, histamine receptor antagonists, proteins and peptides (Page 11, lines 16, 18, Page 12, line 13, page 18, line 11). It is disclosed that the precise quantity of the active ingredient will vary according to the particular drug selected and the patient's needs but that generally the amount will be about 0.2%-95%, typically from about 1% to about 20%, by weight of the composition of the dried dosage form (Page 19, lines 1-5). Examples are disclosed containing fish gelatin and mannitol formed in pre-formed blister pockets (Page 19, lines 1-20, page 20, lines 1-5).

Roser et al. disclose rapidly soluble tablets, such as molded tablets or tablet triturates that contain trehalose and can contain binders such as starch, gelatin, sugars, gum, wherein the active ingredients include antihistaminics, proteins, natural peptides, antigens, etc. (Abstract, Columns 7, 8).

Cho et al. disclose that addition of mannitol stabilized protein against conformational changes in the presence of adjuvants such as aluminum oxyhdroxide or aluminum phosphate (Abstract).

Remington's disclose that although there are exceptions, 90% of labeled potency is generally recognized as the minimum acceptable potency level (Page 1478). It is disclosed that physical factors such as heat and moisture can initiate or accelerate chemical reactions (Page 1475). It is disclosed that uniformity of weight, odor, texture, drug and moisture contents and humidity effect are studied during a tablet stability test (Page 1480). It is disclosed that traditionally extensive stability data are collected at the recommended storage temperatures but that elevated temperatures are very valuable in determining the shelf life of a product (Page

1483). It is disclosed that stable tablets retain their original size, shape, weight and color under normal handling and storage conditions through out their shelf life and the in vitro availability of the active ingredients should not change appreciably over time; hence, the effect of mild, uniform and reproducible shaking and tumbling of tablets should be studied (Page 1480).

Cleland et al. disclose that to obtain desired stability during storage for up to 2 years, proteins are often dried to reduce the rate of chemical and physical degradation (Page 311). It is disclosed that sugars have the ability to stabilize proteins during lyophilization and storage (Page 311). It is disclosed the lyophilized cakes preapred and studied had a residual moisture content of 2% or less (Page 312). It is disclosed that the storage of a mannitol containing formulation resulted in less aggregation when the protein was stored at 40 degrees Celsius for 3 months than formulations without sugar, although slightly less than the same concentration of sucrose or trehalose (Page 314). It is disclosed that mannitol can be combined with other sugars such as sucrose or trehalose (Pages 314-316). It is disclosed that the impact of 1-8.4 % residual moisture was studied and it was determined that there was no effect of residual moisture on aggregation during storage at 2-8 or 40 degrees Celsius for 12 months (Page 316). It is disclosed that when sugars were not present in the formulation there were immediate losses to the protein due to chemical degradation whereas addition of sugar prevented or inhibited degradation over the range of residual moisture levels but that at 8.4 % residual moisture the rate of degradation was increased, yielding a 19% decrease in the main peak of the protein after 12 months at 40 degrees Celsius (Pages 318, 319).

Pradalier et al. disclose that sublingual tablets have been developed as safer and easier to use formulation for immunotherapy of seasonal rhinoconjunctivitis, asthma and perennial rhinitis

(Page 820). The patients in the study were diagnosed with grass pollen season rhinitis, in which some of the patients also had allergic conjunctivitis and mild asthma (Page 820). It is disclosed that the standardized five grass pollen extract was a mixture of orchard grass, meadow grass, ryegrass, sweet vernal grass and timothy grass pollens and that the amount of timothy major allergen in 100 IR/ml extract was 9.5 micrograms/ml (Page 821). It is disclosed that the sublingual route of administration was safe and provided clinical benefits including significant improvements in conjunctivitis symptoms and asthma symptoms (Page 828).

Hordijk et al disclose that patients given 9500 BU of grass pollen extract sublingually resulted in reduction in the severity of allergic complaints (Page 1/12).

WO 00/61117 discloses a fast dispersing molded dosage form comprising a matrix carrier for active agents, such as antihistamines and proteins, containing fish gelatin and other components such as mannitol which dissolves is less than 60 seconds in the mouth. The difference between WO 00/61117 and the claimed invention is that WO 00/61117 does not expressly disclose that the active ingredient is grass pollen allergen where the loss of the allergen content in said dosage form is less than 50% of the initial allergen content after being held for 3 months at 25 degrees Celsius and 60% relative humidity and the loss of allergen content is less than about 0.6 micrograms allergen extract or less than about 0.05 micrograms major allergen when subjected to friability test. However, the prior art amply suggests the same as Remington's discloses that product stability is desired in terms of stability, including storage stability, of the active ingredient and solid dosage formulation when the product is subject to handling and transport, humidity and increased temperatures and . Further, Cho et al. and Cleland et al. disclose that addition of sugars such as mannitol prevent or inhibit protein degradation and

aggregation in the presence of moisture and increased temperature. Also, Pradalier and Hordijk et al. disclose oral administration of grass pollen allergens are effective in immunotherapy of grass pollen allergies. As such, it would have been well within the skill of and one of ordinary skill in the art would have been motivated to combine and/or modify the prior art as above with the expectation that use of mannitol would inhibit degradation over time of the grass pollen allergen extract in the presence of increased temperatures and humidity, that preparation of solid dosage forms which are stable to shaking and tumbling would inhibit loss of grass pollen allergen extract during handling and transportation and that oral administration of grass pollen allergen extract would be effective for immunotherapy of grass pollen allergies.

The Examiner has duly considered the Applicant's arguments but deems them unpersuasive.

The Supreme Court in *KSR International Co. v. Teleflex Inc.*, held the following:

(1) the obviousness analysis need not seek out precise teachings directed to the subject matter of the challenged claim and can take into account the inferences and creative steps that one of ordinary skill in the art would employ;

(2) the obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents;

(3) it is error to look only the problem the patentee was trying to solve-any need or problem known in the filed of endeavor at the time of invention and addressed by the prior art can provide a reason for combining the elements in the manner claimed;

(4) it is error to assume that one of ordinary skill in the art in attempting to solve a problem will be led only to those elements of prior art designed to solve the same problem-common sense teaches that familiar items may have obvious uses beyond their primary purposes, and in many cases one of ordinary skill in the art will be able to fit the teachings of multiple patents together like pieces of a puzzle (one of ordinary skill in the art is not automaton);

(5) it is error to assume that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try". *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396, 1397 (U.S. 2007).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Further, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

The applicant argues that Pradalier and Hordijk et al. discloses administration by sublingual drops while the claimed invention is directed to solid dosage forms. However, the mechanism of action is the same the dosage is administered to the mucosal tissues. However, the Pradalier also discloses the use of sublingual tablets for administration of allergans. As such, solid oral mucosal dosage forms to administer allergens are suggested by the prior art. With

respect to the Applicant's argument as to the use of the same dose in each dosage form. although the prior art discloses increasing dosages, the Applicant acknowledges that maintenance doses are disclosed by the prior art. As such, one of ordinary skill in the art would have prepared solid oral mucosal dosage forms containing the same dosage so as to provide products which were useful for maintenance dosing.

In response to applicant's argument that the examiner has combined an excessive number of references, reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991). The mere fact that seven references are used does not overcome the rejection. Further, there is no requirement that there be an express motivation to combine the references. Nonetheless, the Examiner has provided the reasoning to combine the references as indicated above.

Contrary to the Applicant's arguments, the prior art does suggest a kit. The kit claims require that the dosage form be contained in a sealed container. WO 00/61117, as indicated above, disclose solid oral mucosal dosage forms can be contained in preformed blister pockets. As such, the prior art does suggests kits containing solid oral mucosal dosage forms in a sealed container.

Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention has been collectively taught by the combined teachings of the references.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

A facsimile center has been established in Technology Center 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier number for accessing the facsimile machine is 571-273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Choi whose telephone number is (571)272-0610. Examiner maintains a compressed schedule and may be reached Monday, Tuesday, Wednesday and Thursday, 6:00 am – 4:30 pm (EST).

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, Johann R. Richter, can be reached at (571)272-0646. Additionally, Technology Center 1600's Receptionist and Customer Service can be reached at (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Frank Choi
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January 21, 2010

/Johann R. Richter/
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